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Meiosis Researchers Exchange Information in the Alps

Meeting Review

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An intellectual is a person who has discovered something more interesting than sex.

—Aldous Huxley

The 6th European Meiosis Workshop, sponsored by EMBO and organized by Franz Klein of the University of Vienna, met in mid-September. More than 150 participants who have not discovered anything more interesting than sex gathered in a bucolic Alpine valley near the town of Obertraun, Austria, surrounded by granite massifs.

Meiosis is central and essential to sexual reproduction. Errors in this intricate process are a major source of human birth defects, and the field has consequently been driven by contributions from a diverse range of clinical and basic researchers. New insights at this conference came from molecular geneticists and biochemists investigating the nuts and bolts of DNA breakage, strand exchange, and repair. There were beautiful presentations by cytologists who are elucidating the control of large-scale meiotic chromosome dynamics. We also heard some fascinating perspectives on the evolutionary basis for the very existence of meiosis, which underlies the reassortment of genetic traits and genomic change. Through these synergistic approaches, progress in understanding the coordination of the meiotic cell cycle, chromosome reorganization and recombination, and cellular differentiation programs has been accelerating at a remarkable pace.

The Role of the Synaptonemal Complex in Meiotic Chromosome Behavior

Accurate segregation of chromosomes during meiosis entails several unique feats not required during mitosis. Most conspicuous among these is the physical alignment that occurs between each pair of chromosomes, usually culminating in the formation of a protein polymer called the Synaptonemal Complex (SC) between paired homologs. These intimate contacts enable the maternal and paternal copies of each chromosome to exchange genetic information through crossover recombination. Although the molecular building blocks of the SC have been steadily identified through work in several organisms, the raison d'etre of this meiosis-specific structure has remained a hotly debated question. Does it merely serve to cement the attraction between homologous chromosomes? Is it a structural framework that regulates interhomolog recombination? Why does the SC appear to be dispensable for reciprocal recombination in some systems, such as budding and fission yeast, while its proper formation is a prerequisite for crossovers in other organisms? These questions have been difficult to put to rest for a variety of reasons. One complication is that defects in SC formation lead to meiotic cell cycle arrest and/or apoptosis in many organisms, making it difficult to pinpoint the direct downstream consequences of these aberrations.

Progress in this area was reported by Nancy Kleckner, whose group has carefully re-examined the effects of several key meiotic mutations that alter recombination levels in budding yeast under conditions of high and low temperature. This analysis has led to the far-reaching conclusion that the outcome of recombination events is determined very early during the recombination process, perhaps at the initial step of DNA scission. Furthermore, temperature dramatically modulates this decision-making process, in collaboration with specific meiotic proteins. Kleckner suggested that these effects are likely to be direct consequences of the direct effects of temperature on chromatin strucutre. The concept that important events of meiosis are modulated by nongenetic factors was also underscored by work from Christer Höög's group, who showed that the consequences of removing a specific SC component in mice, SCP3, are strongly modulated by other factors, one being maternal age. This observation is striking in light of the well-known increase in aneuploid pregnancy rate seen among older human mothers.

Although meiosis is a highly conserved process, comparative studies have highlighted informative variations in the precise regulatory mechanisms used by different species. One important distinction separates species into two groups: those that do and those that do not rely on recombination to form the Synaptonemal Complex, which stabilizes contacts between homologous chromosomes (reviewed by Page and Hawley, 2003). Hop2, initially discovered by Shirleen Roeder's lab in budding yeast (Leu et al., 1998), is a still-enigmatic protein that plays a key role in coordinating recombination and synapsis. Daniel Camerini-Otero has now found that Hop2-deficient mice also have synapsis defects, and he has demonstrated biochemically that this protein possesses activities consistent with a direct role in mediating interhomolog interactions. Several conference participants also noted that metazoans such as fruit flies and nematodes, which accomplish chromosome synapsis independently of recombination, have apparently lost both Hop2 and its partner Mnd1.

Striking microscopic images elucidating the ordered assembly and disassembly of the SC had a high impact at this meeting. Immunolocalization studies by Denise Zickler in the fungus *Sordaria*, Julio Rufas in grasshopper spermatocytes, and Gareth Jones in *Arabidopsis* have analyzed specific protein components of the SC in carefully staged meiotic nuclei. Each of these rather

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untraditional cytological systems has provided unique contributions to our appreciation of the Synaptonemal Complex as a dynamic, multifunctional scaffold, rather than the monolith it once seemed. New and sometimes surprising proteins have recently been shown to associate with the SC. For example, Edyta Marcon and Peter Moens reported the localization of an RNA binding protein, MIWI, to the SC in mice. Curiously, Denise Zickler reported that a protein implicated in RNA metabolism is also important for SC formation in *Sordaria* (Tesse et al., 2003). Hints about special roles for RNA in meiosis have been the subject of perennial speculation (e.g., Cook, 1997; Hotta and Stern, 1981), but only occasional experimentation. These new discoveries, along with recent evidence linking RNA to many unforeseen roles in chromosome organization (reviewed by Dernburg and Karpen, 2002; Jenuwein, 2002), will likely stimulate exploration of potential involvement of RNA in meiosis-specific events such as pairing and recombination.

Entry into Meiosis Is Controlled by RNA Regulators

A theme emerging from studies in widely divergent organisms is that the regulation of meiotic gene expression, and thus meiotic progression, has unusual and critical posttranscriptional components. In fission yeast this is evident from Masayuki Yamamoto's analysis of Mei2p, an essential RNA binding regulator (Yamashita et al., 1998), which has led to the discovery of a sequence element common to transcripts of several meiotic genes that causes them to be rapidly degraded in vegetative cells. A multipronged RNA regulatory pathway controlling meiotic entry is also being elucidated in *C. elegans* by Judith Kimble's lab, and their latest results were presented by Sarah Crittenden. This pathway affects both the stability and the translational efficiency of specific mRNAs, in part through modulation of the length of poly(A) tails (Crittenden et al., 2003; Wang et al., 2002). Future work will likely reveal how widely these mechanisms are conserved and whether they might be functionally related to the evolutionary origins of meiosis.

Expanding Roles for Heterochromatin in Meiotic Chromosome Segregation

In addition to achieving homolog pairing and recombination, meiotic chromosomes must interact with the segregation machinery in special ways. By contrast to mitosis, sister chromatids must stay together rather than separating during the first meiotic division, and sister kinetochores must attach to the same spindle pole, while homologs attach to opposite poles. Kim Nasmyth's group first identified molecules that ensure that sister centromeres orient toward the same pole in budding yeast and named this complex "monopolin" (Rabitsch et al., 2003; Toth et al., 2000). Now Yoshinori Watanabe's group has identified a novel protein in fission yeast, Moa1, that seems to have a function analogous to the monopolin complex, although it does not share apparent sequence similarity. The Watanabe group has also carried out an elegant genetic screen based on the idea that mitotic chromosome segregation would be compromised if meiosis-specific modes of centromere behavior were inappropriately activated. He reported on the fruits of this analysis, which has identified a novel protein that ensures that the sisters do not come apart until the appropriate time by inhibiting degradation of the meiotic cohesin Rec8. He has named this gene Sgo1 (Shugoshin, Japanese for "guardian spirit"), although it was tentatively referred to as Prt1 at the meeting. Surprisingly, he suggested that this guardian protein shares distant sequence similarity with *Drosophila* protein MEI-S332, as well as potential mammalian homologs. Sgo1 associates with the heterochromatic regions flanking the kinetochore, rather than the central core of the centromere, as has also been shown for MEI-S332 (Blower and Karpen, 2001). These observations suggest that in widespread species, a heterochromatin-associated protein serves to protect cohesin from degradation near centromeres during meiosis I.

Further indications of the contribution of heterochromatin in orchestrating meiotic chromosome behavior came from new studies in *Drosophila*. Scott Hawley reported the discovery of a protein called Matrimony (Mtrm) that holds homologous chromosomes together and may promote their proper orientation on the spindle. He has found that this protein localizes to the pericentric heterochromatin of fly chromosomes during meiosis and that reduction in the amount of this protein results in major defects in chromosome segregation. Gunter Reuter examined the meiotic effects of mutations in genes known as Su(var)s, which modulate heterochromatin-mediated transcriptional silencing in *Drosophila* (Westphal and Reuter, 2002). Several of these mutations permit recombination to occur in the repetitive regions near the centromeres, which are usually precluded from crossing over during meiosis. Dramatic increases in crossing-over were also detected in the neighboring euchromatic regions, which normally recombine at low rates due to the suppressive effects of the nearby heterochromatin. Because the effects of different Su(var) mutations are additive, he surmises that the suppression of recombination results from this specialized chromatin organization, which is the net result of this constellation of gene products. Surprisingly, many of these mutations actually reduce the missegregation rate in females, which seems counterintuitive since it implies that meiotic chromosome segregation is not normally as error-free as it could be. Reuter suggested that heterochromatin may be maintained through evolution to optimize the balance between crossover formation and accurate segregation. He also noted that meiosis in older female flies is more acutely affected by these mutations, perhaps another example of the interplay between aging cellular physiology and structural components of meiotic chromosomes.

Evolutionary Origins and Maintenance of Meiosis

One enigma that has long been a subject of discussion in the field is why meiosis exists in the first place. Clearly this mechanism of chromosome reduction is essential for sexual reproduction as we know it, but this is no chicken and egg paradox—meiosis does not require sex, and it occurs independent of mating in hermaphrodites and parthenogenic females. Population biologists have wrestled to account for the near-ubiquity of sex among eukaryotes—indeed, the costs of this rather messy process often seem to exceed its advantages,

when assessed dispassionately and mathematically. Insights from two evolutionary biologists stimulated much conversation at this meeting. Thomas Cavalier-Smith suggested that meiosis may have originated as a mechanism to restore the proper number of chromosomes if an aberrant genome duplication event occurred during the process of chromosome replication and segregation. His analysis of the evolutionary tree indicates that the primordial eukaryote was able to carry out both mitosis and meiosis and that these processes thus coevolved rather than one being derived from the other (Cavalier-Smith, 2002). Matthew Meselson has taken an unusual route to understanding the importance of meiosis: his group studies a group of rotifers, small eukaryotes that have mysteriously lost the ability to carry out meiosis yet have continued to diverge and even to speciate. His presentation also highlighted evidence from other organisms, such as fungi and ciliates, that meiosis may serve as a defense against mobile DNA elements by providing an opportunity for an organism to compare two copies of its genome in order to inactivate or even remove regions of nonhomology. Paradoxically, however, sex may also have given mobile elements even richer opportunities to spread, at least for any element clever enough to replicate itself in the germline. Both of these presentations supported the notion that the evolution of meiosis did not mark the beginning of the arms race, but probably led to a rapid proliferation in the variety and ingenuity of both the mobilization mechanisms of selfish genetic elements and hosts' defenses against them.

Meiosis: Twenty Years of Molecular Biology

This year marks the 20th anniversary of a landmark paper proposing a model for meiotic recombination based on DNA repair mechanisms (Szostak et al., 1983). Although meiosis was first described well over a century ago, molecular understanding of this process has emerged almost entirely from work done in the two decades since that paper was published. Technological advances in microscopy, large-scale analysis of gene expression, chemical genetics, and gene disruption methods are all being harnessed by this research community to achieve an integrated understanding of this process. The next EMBO Meiosis Workshop, planned for 2005 in Spain, will undoubtedly be another stimulating opportunity to learn about advances in this dynamic and multifaceted field.

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